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Review

The superfamily of organic anion transporting polypeptides

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Abstract

Organic anion transporting polypeptides (Oatps/OATPs) form a growing gene superfamily and mediate transport of a wide spectrum of amphipathic organic solutes. Different Oatps/OATPs have partially overlapping and partially distinct substrate preferences for organic solutes such as bile salts, steroid conjugates, thyroid hormones, anionic oligopeptides, drugs, toxins and other xenobiotics. While some Oatps/OATPs are preferentially or even selectively expressed in one tissue such as the liver, others are expressed in multiple organs including the blood–brain barrier (BBB), choroid plexus, lung, heart, intestine, kidney, placenta and testis. This review summarizes the actual state of the rapidly expanding OATP superfamily and covers the structural properties, the genomic classification, the phylogenetic relationships and the functional transport characteristics. In addition, we propose a new species independent and open ended nomenclature and classification system, which is based on divergent evolution and agrees with the guidelines of the Human Genome Nomenclature Committee.

Keywords: Drug transporter; Xenobiotic elimination; Bile salt; Liver transport; Brain transport

1. Introduction

Organic anion transporting polypeptides (rodents: Oatps; human: OATPs) are a group of membrane solute carriers with a wide spectrum of amphipathic transport substrates [1,2]. Although some important members of this transporter superfamily are selectively expressed in rodent and human livers, where they are involved in the hepatic clearance of albumin-bound compounds from portal blood plasma [3], most Oatps/OATPs are expressed in multiple tissues including the blood–brain barrier (BBB), choroid plexus, lung, heart, intestine, kidney, placenta and testis [4]. Only a portion of the Oatps/OATPs so far identified has been characterized in detail on the functional, structural and genomic levels. However, initial studies with individual Oatps/OATPs indicate that many members of this transporter family represent polyspecific organic anion carriers with partially overlapping and partially distinct substrate preferences for a wide range of amphipathic organic solutes including bile salts, organic dyes, steroid conjugates, thyroid hormones, anionic oligopeptides, numerous drugs and other xenobiotic compounds [1,2,5]. This overview summarizes the structural properties, genomic classification, phylogenetic relationships and functional transport characteristics of the currently known rodent and human Oatps/OATPs. Furthermore, the article proposes a new nomenclature system that is based on divergent evolution, uses functionally based root symbols, is species independent and open ended, and thus could help to end the current chaotic nomenclature status and to prevent future confusions and misunderstandings regarding the clear identification of individual members of the OATP-superfamily of membrane transporters.

2. Classification of Oatp/OATP genes

Currently, 11 rat, 8 mouse and 9 human Oatps/OATPs have been identified. Their genes are currently classified within the solute carrier family 21A (rodents: *Slc21a*; humans: *SLC21A*) of the human (http://www.gene.ucl.ac.uk/) and mouse (http://www.informatics.jax.org/) genome

Abbreviations: APD-ajmalinium, *N*-(4,4-azo-*n*-pentyl)-21-deoxyajmalinium; APM, azidoprocainamide methoiodide; APQ, *N*-(4,4-azo-*n*-pentyl)-quinuclidine; Bsep, bile salt export pump; BSP, bromosulfophthalein; BSP-GSH, glutathione-conjugated BSP; CCK-8, cholecystokinin-8; DAMGO, D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]-enkephalin; DHEAS, dehydroepiandrosterone-sulfate; DNP-SG, dinitrophenyl-glutathione; DPDPE, [D-Pen^{2,5}]-enkephalin; Gd-B 20790, gadolinium derivative; Ntcp, Na^+/taurocholate cotransporting polypeptide; OAT, organic anion transporters; OATP, organic anion transporting polypeptide; OCT, organic cation transporters

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Table 1
Oatp/*OATP* gene classification as implemented by the human and mouse gene nomenclature committees

Name	Alias	Human gene name	Rat gene name	Mouse gene name
Oatp1	Oatp	–	*Slc21a1*	*Slc21a1*
PGT	hPGT (man), rPGT (rat), mPGT (mouse)	*SLC21A2*	*Slc21a2*	*Slc21a2*
OATP-A	OATP, OATP1	*SLC21A3*	–	–
OAT-K1		–	*Slc21a4*	–
Oatp2		–	*Slc21a5*	*Slc21a5*
OATP-C	LST-1, OATP2, OATP6	*SLC21A6*	–	–
Oatp3		–	*Slc21a7*	*Slc21a7*
OATP8	LST-2	*SLC21A8*	–	–
OATP-B	OATP-RP2 (man), moat1 (rat), **Oatp9**	*SLC21A9*	*Slc21a9*	–
Oatp4	rlst-1 (rat), mlst-1 (mouse)	–	*Slc21a10*	*Slc21a10*
OATP-D	OATP-RP3 (man), Pgt2 (rat), MJAM (mouse), **Oatp11**	*SLC21A11*	*Slc21a11*	*Slc21a11*
OATP-E	OATP-RP1 (man), oatpE (rat), **Oatp12**	*SLC21A12*	*Slc21a12*	–
Oatp5		–	*Slc21a13*	*Slc21a13*
OATP-F	OATP-RP5 (man), BSAT1 (rat), Oatp2 (mouse), **Oatp14**	*SLC21A14*	*Slc21a14*	*Slc21a14*
OATP-J	OATP-RP4	*SLC21A15*	–	–

The aliases in bold will be used in this review for the rat and mouse species if available.

nomenclature databases. As it can be seen from Table 1, with the exception of OATP8 (*SLC21A8*), the trivial names for individual proteins do not correspond to the continuous numbering (based on the chronology of protein identification) within the *Slc21a*/*SLC21A* classification. Furthermore, for many rat/mouse *Oatp* genes no orthologous human *OATP* genes have so far been identified indicating no strict one to one relationship between rodent *Oatps* and human *OATPs* [4]. In addition, different names have been coined on the protein level, which has led to some confusion in the differentiation between certain individual rodent and human Oatps/OATPs, as exemplified in a recent publication where the regulation of the rat/mouse Oatp2 has been erroneously attributed to the non-orthologous human OATP2 [6]. Hence, for clear-cut identification of a specific gene product, it has been suggested to continue with the numbering of rodent Oatps, to adopt provisionally the alphabetic designation of human OATPs and to always add the corresponding *Slc21a*/*SLC21A* gene symbol in parenthesis [4,5]. However, since this nomenclature does still not conform to a species independent and open-ended classification, a more definitive classification system based on divergent evolution (amino acid sequence identities) would be advantageous and is proposed below (see Section 7).

3. Structural characteristics of Oatps/OATPS

Based on hydropathy analysis, all Oatps/OATPs contain 12 transmembrane (TM) domains as indicated in Fig. 1 for rat Oatp1 (*Slc21a1*) [7]. However, it is important to realize that the predicted 12 TM domain model has not been proven experimentally for any Oatp/OATP so far identified. Common structural features among all Oatps/OATPs include (1) the large extracellular domain between TMs 9 and 10 (extracellular loop 5), which contains many conserved cysteine residues that resemble the zinc finger domains of DNA binding proteins [8], (2) the *N*-glycosylation sites in extracellular loops 2 and 5 [9], and (3) the OATP "superfamily signature" (see Fig. 3) at the border between extracellular loop 3 and TM domain 6. Conserved amino acids are preferentially found in TM domains 2 to 6, in extracellular loops 1, 3, 5 and in intracellular loops 1, 2, 4 and 5 (Fig. 1). Conserved charged amino acids are located predominantly at the boundaries of the TM domains, especially on the

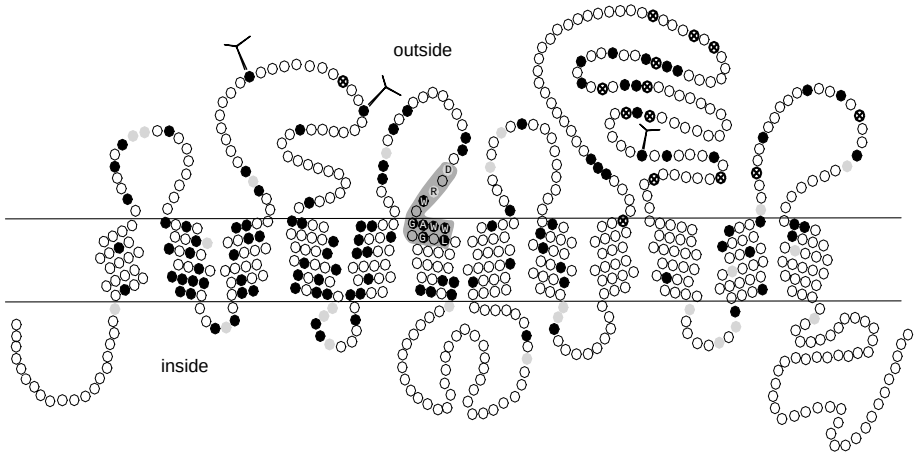

Fig. 1. Predicted 12 transmembrane domain model of rat Oatp1. Conserved amino acids (see Fig. 2) are indicated in black. Conserved and charged amino acids (D, E, K, R) are given in gray, and conserved cysteines (C) are marked with asterisks. Three potential *N*-glycosylation sites (Y) are present on extracellular protein loops. The OATP superfamily signature (see Fig. 3) is indicated at the border of the extracellular loop 3 and the transmembrane domain 6.

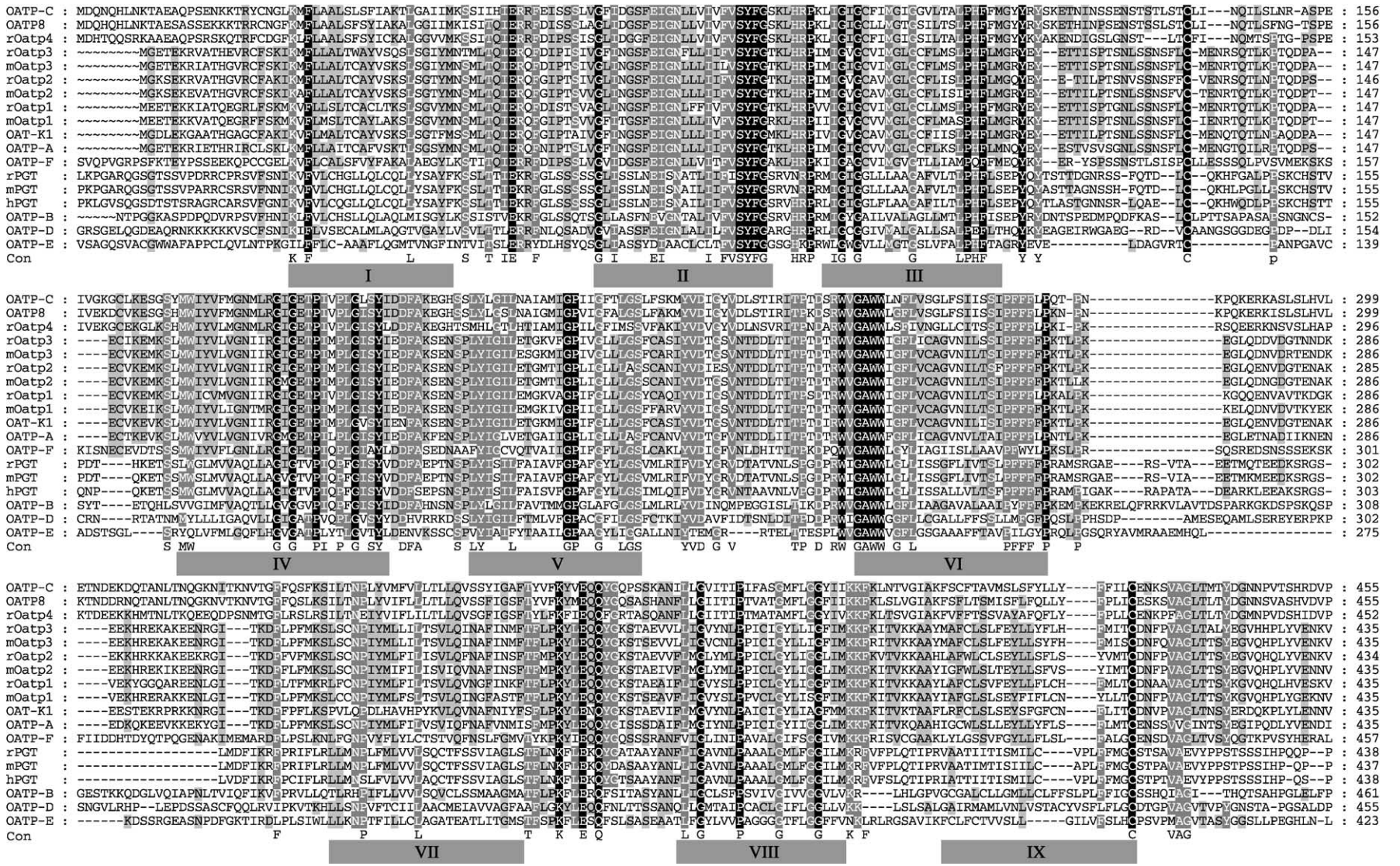

Fig. 2. Multiple alignment of human, rat and mouse Oatps/OATPs. The program PILEUP from the GCG software package (Genetics Computer Group, Madison, WI) [12] was used to align the amino acid sequences of the 18 Oatps/OATPs for which functional transport data are available. Splice variants such as OAT-K2 and rlst-1 were not considered. Positions of the respective amino acid residues are listed for the individual proteins. Note that for some amino acid sequences the alignment does not start at position 1. The consensus sequence (Con) contains amino acid residues that are conserved in at least 15 Oatps/OATPs. Transmembrane domains were estimated with the help of the TMHMM program (http://www.cbs.dtu.dk/services/TMHMM-2.0/) [13]. They are indicated with dark gray bars and numbered continuously in roman numbers.

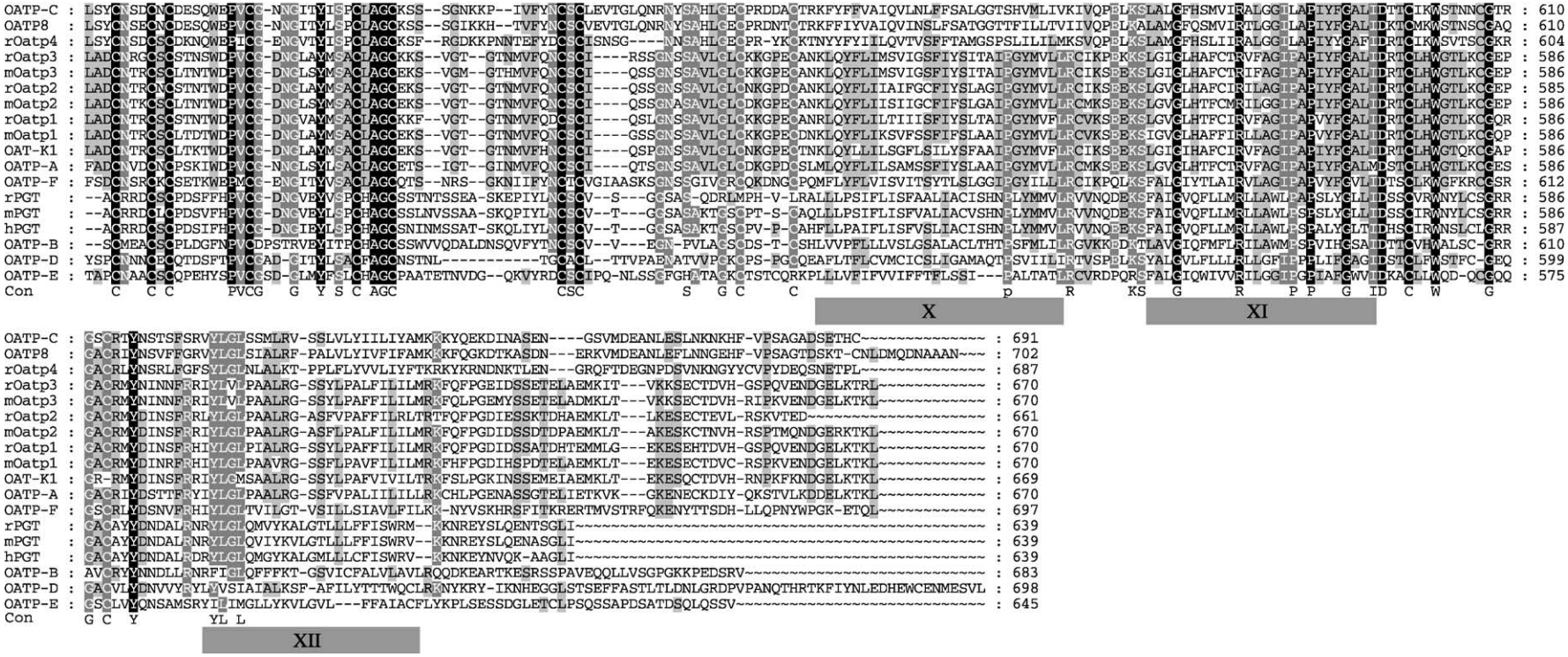

Fig. 2 (*continued*).

cytoplasmic side of the membrane. Within the membrane the only charged amino acids conserved are found in TM domains 2, 11 and 12. The physiological importance of these charged amino acid residues for transmembrane substrate transport will have to be determined by site-directed mutagenesis.

3.1. Multiple amino acid sequence alignment and evolutionary relationship

Fig. 2 compares the amino acid sequences of 18 members of the OATP superfamily. All cloned proteins contain between 643 (rat, mouse and human prostaglandin transporters (PGTs); *Slc21a2*/*SLC21A2*) and 722 (OATP-E; *SLC21A12*) amino acids [4,10,11]. Altogether, 57 amino acid residues have been conserved through all 18 family members. They include 15 glycine, 11 cysteine, 8 proline, 5 tyrosine and 4 tryptophan residues. The glycine and proline residues are important for the protein structure. Glycine has no side chain and gives the polypeptide a much greater flexibility than other residues, whereas proline poses more rigid constrains on the rotational mobility and, thus, stabilizes the tertiary structure of the protein backbone. The conserved cysteine residues are concentrated in the large extracellular loop between TM domains 9 and 10 and are responsible for the supposed zinc finger motif of the Oatps/OATPs [8]. The physiologic significance of the latter is unknown, but it is interesting to note that a portion of the rat prostaglandin transporter rPGT [11] has first been isolated as the DNA-binding protein "matrin F/G" [8], and that several Oatp-related proteins in *C. elegans* and *D. melanogaster* are postulated to represent also zinc finger DNA-binding proteins. Since the sequence of cysteine residues resembles that of the class 2 or C_4 type zinc finger domains that is also found in steroid hormone receptors and since Oatps/OATPs mediate transport of steroid hormones and their conjugates (see below), it is tempting to speculate that this region could be involved in substrate recognition and/or binding.

3.2. Evolutionary relationship

Interestingly, conserved amino acids also include four tryptophan residues, three of which form part of the highly conserved consensus sequence D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the border of extracellular loop 3 and TM domain 6 (Figs. 1–3). If this OATP "superfamily signature" was used to search the Genbank database for related sequences, a total number of 39 Oatp/OATP-related proteins were identified including all known Oatps/OATPs, two new Oatps from *B. taurus* and *R. erinacea* and 12 proteins of unknown function from *C. elegans* and *D. melanogaster* (Fig. 3). However, no bacterial or yeast proteins with significant homologies were found. Intriguingly, all these Oatp/OATP-related proteins contain, in addition to the "superfamily signature", the conserved cysteine residues

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OATP-A                      DTRWVGAWWFGFL
OATP-B                      DPRWIGAWWGGFL
OATP-C                      DSRWVGAWWLNFL
OATP-D                      DPRWIGAWWGGFL
OATP-E                      SPLWVGAWWVGFL
OATP-F                      DPQWVGAWWLGYL
OATP8                       DSRWVGAWWLGFL
OATP-J                      DPRFIGNWWSGFL
hPGT                        DPRWIGAWWLGLL
Rat Oatp1                   DTRWVGAWWIGFL
Rat Oatp2                   DTRWVGAWWIGFL
Rat Oatp3                   DTRWVGAWWIGFL
Rat Oatp4                   DARWVGAWWLSFI
Rat Oatp5                   DTRCVGAWWIGFL
rat Oatp9                   DPRWVGAWWLGFL
Rat Oatp11                  DPRWIGAWWGGFL
Rat Oatp12                  SPLWIGAWWLGFL
Rat Oatp14                  DPQWVGAWWLGYL
Rat OAT-K1                  DIRWVGAWWIGFL
Rat PGT                     DPRWIGAWWLGLL
Mouse Oatp1                 DTRWVGAWWIGFL
Mouse Oatp2                 DTRWVGAWWIGFL
Mouse Oatp3                 DTRWVGAWWIGFL
Mouse Oatp4                 DARWVGAWWLGFI
Mouse Oatp5                 DTRWVGAWWIGFL
Mouse Oatp11                DPRWIGAWWGGFL
Mouse Oatp14                DPQWVGAWWLGYL
Mouse PGT                   DPRWIGAWWLGLL
B. taurus AAL14261          DTRWVGAWWIGFL
R. erinacea AAL66021        DARWVGAWWIGFL
C. elegans CAA21751         DPRWVGAWWVGFI
C. elegans CAB02665         DEHWIGAWWLGFL
C. elegans AAB52651         DPTWVGAWWLSFI
D. melanogaster AAF46824    DPRWLGAWWLGWL
D. melanogaster AAF46825    DPRWMGAWWIGWI
D. melanogaster AAF46826    DPRWLGAWWLGWL
D. melanogaster AAF49332    DPRWIGAWWLGPV
D. melanogaster AAF53195    DPRWLGAWWLGWV
D. melanogaster AAG22418    SKVWIGAWWLGFI

Consensus                   DTRWVGAWWIGFL
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Fig. 3. Multiple alignment of the OATP-superfamily signature. The consensus sequence was used to BLAST the GenBank database. Besides the known mammalian OATPs several potential organic anion transporters from *C. elegans*, *D. melanogaster*, *B. taurus* and *R. erinacea* were identified and are indicated with their protein accession numbers.

in the extracellular loop between TMs 9 and 10 (data not shown), thus supporting further the evolutionary relationship of the various proteins. However, whether all Oatp/OATP-related proteins including the superfamily members of *C. elegans* and *D. melanogaster* represent multispecific membrane transporters remains to be verified.

The overall amino acid sequence identities between all Oatp/OATP-related proteins summarized in Fig. 3 vary between 24% and 82% (calculated by BESTFIT). Hence, based on this amino acid sequence identities, all Oatp/OATP-related proteins form a gene superfamily that spans a wide range of animal species. Considering only mammalian Oatps/OATPs, the amino acid sequence identities vary between 31% and 82% (Table 2). If one arranges these amino acid sequence identities into groups of decreasing identities, it becomes evident that individual proteins cluster into families ($\geq$40% identity) and subfamilies ($\geq$60%

Table 2
Amino acid sequence identities among the different members of the OATP superfamily

	OATP-A	rOatp1	mOatp1	rOatp2	mOatp2	rOatp3	mOatp3	rOatp5	mOatp5	OATK1	OATP-C	OATP8	rOatp4	mOatp4
OATP-A	100	67	69	73	73	72	73	66	67	66	44	42	42	41
rOatp1		100	81	77	78	80	81	74	72	72	44	46	43	43
mOatp1			100	78	80	80	81	75	74	75	46	46	44	44
rOatp2				100	89	82	83	77	76	77	46	45	44	43
mOatp2					100	83	84	77	75	77	45	44	44	42
rOatp3						100	92	76	76	79	46	46	44	44
mOatp3							100	78	77	78	45	47	44	44
rOatp5								100	80	73	45	46	44	43
mOatp5									100	71	45	46	43	42
OATK1										100	46	43	43	42
OATP-C											100	80	64	65
OATP8												100	66	67
rOatp4													100	82
mOatp4														100
OATP-F														
rOatp14														
mOatp14														
hPGT														
rPGT														
mPGT														
OATP-B														
rOatp9														
OATP-D														
rOatp11														
mOatp11														
OATP-E														
rOatp12														
OATP-J														

Amino acid sequence identities were calculated using the GCG program BESTFIT. Identities above 60% are printed in white on black, identities between 40% and 60% are printed in white on gray while identities below 40% are printed in black on white. The 28 Oatps/OATPs presented in Table 1 are shown.

identities) as it has been previously shown for drug metabolizing enzymes [14–16]. Interestingly, the members of the OATP3-family (i.e. rOatp11, mOatp11, OATP-D) show the highest conservation with amino acid identities of 97% and 98% among rat, mouse and human proteins (Table 2). The clustering of individual Oatps/OATPs into families and subfamilies is further evident from the phylogenetic tree (Fig. 4). Thereby, the proteins with the broadest spectrum of amphipathic transport substrates are clustered in the large OATP1 family. These OATP1-family members are thought to be part of the overall body detoxification system and help to remove potentially toxic endo- and xenobiotics from the systemic circulation (e.g. drug uptake into the liver) [1]. Although the exact physiological functions of most Oatps/OATPs remain to be elucidated, most Oatps/OATPs of families 2–4 have narrower substrate specificities (e.g. OATP-B, OATP-E) and may serve more specific functions in selected organs such as for example thyroid hormone transport in various peripheral organs [18] or steroid and steroid metabolite transport in adrenal gland and placenta [19,20]. Thus, the functional diversity of the OATP superfamily could be very similar to the *CYP450* superfamily where only families 1–4 are involved in metabolism and detoxification of drugs and environmental chemicals, whereas the members of the other families catalyze specific pathways in the cholesterol, prostacyclin and/or steroid metabolism [16].

3.3. Chromosomal localization

Based on the available human genome data, all human OATP genes could be mapped on the genomic level and are located on chromosomes 3 (*SLC21A2*), 8 (*SLC21A15*), 11 (*SLC21A9*), 12 (*SLC21A14, SLC21A8*, *SLC21A6* and *SLC21A3* in this order), 15 (*SLC21A11*) and 20 (*SLC21A12*). The human OATP1 family members are not only located all on chromosome 12 but are clustered at 12p12 on a stretch of approximately 700,000 bp. The smallest gene is *SLC21A14* (OATP-F) and covers about 58,000 bp followed by *SLC21A3* (OATP-A 66,000 bp), *SLC21A6* (OATP-C 98,000 bp) and SLC21A8 (OATP8 101,000 bp). Between *SLC21A8* and *SLC21A6* a pseudogene of approximately 172,000 bp can be found. This type of clustering indicates that these OATPs have arisen through gene duplications of an ancestral gene. Given almost identical lengths of the respective exons in the different OATPs [21], it is tempting to speculate that the newer a gene, the longer the intronic sequences. This would suggest that OATP-F represents the oldest OATP in this family and that the pseudogene represents the last addition. This assumption is supported by the recent identification of the first and so far only OATP in the liver of the little skate that shares the highest amino acid identity with OATP-F and transports a wide range of different compounds [22]. Sequencing of the mouse genome is also very advanced and

OATP-F	rOatp14	mOatp14	hPGT	rPGT	mPGT	OATP-B	rOatp9	OATP-D	rOatp11	mOatp11	OATP-E	rOatp12	OATP-J
48	48	48	38	37	36	34	34	36	36	36	32	33	34
48	47	47	38	39	39	35	34	36	36	35	35	34	35
48	48	49	38	37	37	33	34	38	39	39	34	34	35
47	46	48	36	37	37	33	33	37	37	38	35	34	35
46	47	46	38	37	37	32	32	36	38	38	34	34	34
47	46	46	36	37	37	34	33	38	38	38	34	35	35
48	46	46	37	37	37	35	33	37	37	37	34	34	36
44	44	45	37	37	36	34	34	34	35	34	36	35	34
46	45	45	37	37	36	35	35	37	37	38	34	34	35
45	44	44	38	37	36	32	32	36	36	36	34	35	32
47	47	46	36	35	38	35	36	37	38	39	31	33	37
48	46	47	36	36	36	35	35	36	36	37	34	33	37
45	44	43	33	33	34	33	33	36	36	36	31	33	36
45	46	44	35	35	35	35	34	35	36	36	32	34	35
100	85	84	36	35	35	34	34	37	36	37	34	34	34
	100	95	36	36	36	34	34	37	38	37	35	35	34
		100	36	36	36	35	33	36	36	35	34	34	33
			100	82	83	48	48	39	39	39	35	33	36
				100	91	47	48	37	37	37	34	33	34
					100	47	49	37	37	37	35	35	35
						100	77	36	35	35	34	34	36
							100	37	37	37	32	34	36
								100	97	97	38	35	39
									100	98	37	36	38
										100	38	36	38
											100	76	41
												100	39
													100

huge continuous clusters can be compared to the human syntenic regions. Interestingly, all mouse OATP1 family members can be located on an approximately 800,000 bp cluster on mouse chromosome 6 (including *Slc21a1*, which, using fluorescence in situ hybridization, has previously been mapped to chromosome X [23]) in a similar order

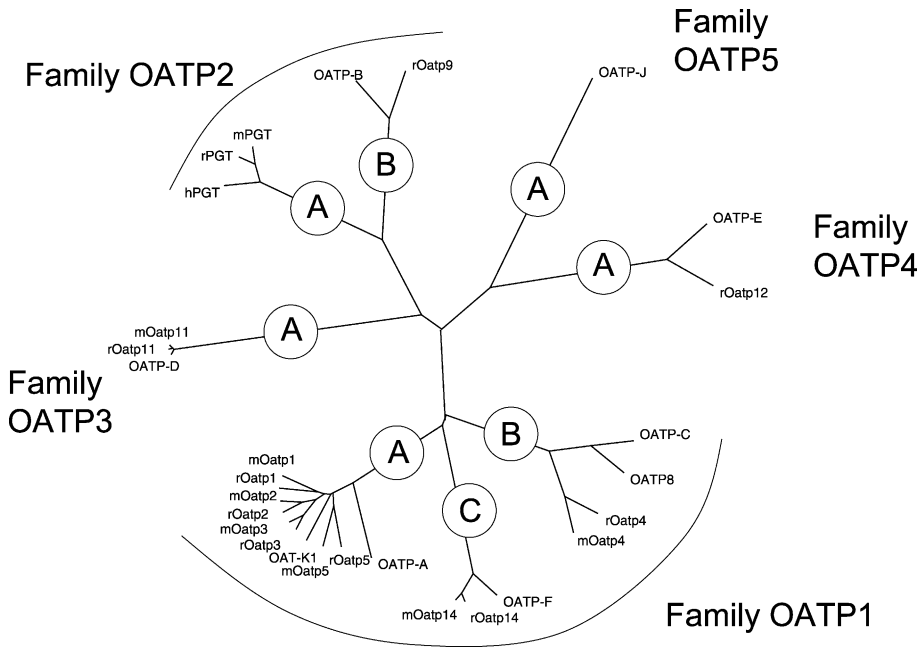

Fig. 4. Phylogenetic tree of the mammalian Oatps/OATPs. The phylogenetic tree was calculated using GCG programs PILEUP, DISTANCES and GROWTREE and visualized using the program TreeView [17]. The individual families contain proteins with amino acid sequence identities of $\geq 40\%$. Subfamilies are indicated by capital letters and contain proteins with amino acid sequence identities of $\geq 60\%$.

as the human genes (*Slc21a14*, *Slc21a10*, *Slc21a13*, *Slc21a5*, *Slc21a1* and *Slc21a7*). This comparison clearly suggests that there is no single orthologue of the human OATP-A in the mouse (Oatp1, Oatp2, Oatp3 and Oatp5) and no single orthologue of the mouse Oatp4 in man (OATP-C and OATP8). All the other so far known mouse Oatp genes can also be mapped to syntenic chromosomes in man.

4. Functional properties of Oatps/OATPs

4.1. Broad spectrum of transported substrates

Originally, Oatp1 has been cloned as a sodium-independent bromosulfophthalein (BSP) and taurocholate uptake system of rat liver [7,24,25]. However, later it has been shown that Oatp1 can mediate transmembrane transport of a wide range of amphipathic organic compounds including bile salts [26–28], steroid hormones and their conjugates [27–31], thyroid hormones [32], and even organic cations like *N*-(4,4-azo-*n*-pentyl)-21-deoxy-ajmalinium [29,33] and to a lesser degree also *N*-methyl-quinine and rocuronium [33] (Table 3). Such a broad and partially overlapping substrate specificity has also been documented for other Oatps/OATPs (Table 3). In addition to endogenous and exogenous amphipathic compounds, Oatps/OATPs can mediate transport of numerous drugs including the endothelin receptor antagonist BQ-123 [28], the thrombin inhibitor CRC-220 [34], the opioid receptor agonists [D-penicillamine 2,5]enkephalin (DPDPE) and deltorphin II [35], the angiotensin-converting enzyme inhibitors enalapril and temocaprilat [36,37], the HMG-CoA reductase inhibitor pravastatin [38] and the antihistamine fexofenadine [39] (Table 3). Therefore, these multispecific transporters (especially the members of the OATP1A and 1B subfamilies (Fig. 4, Table 3)) are important drug transporters that, together with the P-glycoproteins and the multidrug resistance associated proteins (Mrps), seem to play an important role in overall drug absorption and drug disposition. Since not all substrates have been tested with all Oatps/OATPs, only a few "specific" substrates could be identified so far (e.g. gadoxetate and dinitrophenyl-glutathione (DNP-SG) for Oatp1, bilirubin and bisglucuronosyl bilirubin for OATP-C, CCK-8 for the rat Oatp4 and the human OATP8). However, differences in substrate transport have been documented with respect to apparent affinities: Oatp2 is a high affinity digoxin transporter (apparent $K_m = 0.24$ μM) [40], OAT-K1 a high affinity methotrexate carrier (apparent $K_m = 1$ μM) [41] and OATP-F a high affinity T_4 and rT_3 transporter [21].

What are the chemical/structural requirements for a compound to be transported by Oatps/OATPs? So far no systematic studies have been performed to investigate this but from the data summarized in Table 3, it can be concluded that in general Oatp/OATP substrates are mainly anionic amphipathic molecules with high molecular weight (>450) that under normal physiological conditions (with few exceptions as e.g. gadoxetate) are bound to proteins (mostly albumin). Or more specifically, compounds with a steroid nucleus (e.g. bile salts, steroid hormones and their conjugates) or small linear and cyclic peptides are likely candidates to be transported by certain Oatps/OATPs. These are also the attributes of compounds that are mainly excreted into bile while products that are normally excreted into urine are represented by small and mainly hydrophilic compounds with low protein binding and are known substrates of the organic anion (OATs) and organic cation transporters (OCTs) [42,43]. However, for a more exact determination of the structural requirements of Oatp/OATP substrates, additional experiments are required.

4.2. Transport mode

Unlike the Na^+/taurocholate cotransporting polypeptide (Ntcp/NTCP), which couples downhill sodium import to uphill bile salt uptake [75,76], it is well accepted that Oatps/OATPs represent sodium-independent bile salt and organic anion transport systems [7,40,57,64]. Their transport mechanism appears to be anion exchange as evidenced by bidirectional transmembrane BSP transport in Oatp1 expressing HeLa cells [25] and by Oatp1-mediated taurocholate/HCO_3 exchange [44]. The driving force for Oatp/OATP-mediated transport has not been investigated in detail for all transporters, but for Oatp1 and Oatp2 there exists experimental evidence that intracellular GSH plays an important role. Oatp1-expressing oocytes showed increased [^{3}H]glutathione (GSH) efflux and a stoichiometry of GSH/taurocholate exchange of 1:1, indicating that Oatp1 participates in overall GSH efflux from hepatocytes [45]. Hence, physiologic GSH efflux could represent an important driving force for Oatp1-mediated substrate uptake into hepatocytes as well as into choroid plexus epithelial cells [77]. Similar to Oatp1, Oatp2-mediated taurocholate transport was also stimulated by high intracellular GSH concentrations [78]. However, simultaneous changes of the extracellular GSH concentration did not affect Oatp2 mediated substrate transport suggesting that intracellular GSH rather than the in to out GSH gradient is important for Oatp2 mediated taurocholate uptake [78]. Additional evidence for an asymmetric transport mechanism of Oatp2 was derived from the observation that Oatp2 expressing oocytes were not able to accumulate radiolabeled DNP-SG from the extracellular medium, whereas high intracellular concentrations of DNP-SG stimulated Oatp2-mediated taurocholate uptake [78]. If we assume such an asymmetric transporter mode for all Oatps/OATPs, intracellular GSH may be also important for OATP8-mediated transport although extracellular GSH did not cis-inhibit OATP8-mediated BSP uptake nor was it transported into OATP8 expressing HEK293 cells [74].

Table 3
Molecular characteristics of the members of the OATP superfamily

Transporter	Size[a]	Substrates (K_m value)	Main location	References
Rat Oatps				
Oatp1 (*Slc21a1*)	670	*Bile salts*: cholate (54 μM), glycocholate (54 μM), taurocholate (19–50 μM), TCDCA (7 μM), TUDCA (13 μM), sulfotaurolithocholate (6 μM). *Hormones and their conjugates*: aldosterone (15 nM), cortisol (13 μM), DHEAS (5 μM), $E_2$17βG (3–20 μM), E-3-S (5–12 μM), T_3, rT_3, T_4. *Eicosanoids*: LTC_4 (270 nM). *Peptides*: BQ-123 (600 μM), CRC220 (30–57 μM), deltorphin II (137 μM), DPDPE (48 μM), GSH. *Drugs*: dexamethasone, enalapril (214 μM), fexofenadine (32 μM), gadoxetate (3.3 mM), ouabain (1.7–3 mM), pravastatin (30 μM), temocaprilat (47 μM). *Other organic anions*: monoglucuronosyl bilirubin, BSP (1–3 μM), BSP-DNP-SG (408 μM), E3040 glucuronide. *Organic cations*: APD-ajmalinium, *N*-methylquinidine, rocuronium. *Toxins*: ochratoxin A (17–29 μM).	mRNA: liver, kidney, brain, lung, retina, skeletal muscle, proximal colon Protein: liver, kidney, choroid plexus (?)	[7,25–29, 31–39,44–49]
rPGT (*Slc21a2*)	643	*Eicosanoids*: 6-ketoprostaglandine $F_{1\alpha}$ (6 μM), prostaglandine D_2, prostaglandine E_1 (70 nM), prostaglandine E_2 (94 nM), prostaglandine $E_{2\alpha}$ (104 nM), thromboxane B_2 (423 nM).	Ubiquitously	[10,11]
OAT-K1/2 (*Slc21a4*)	669/498	*Bile salts*: taurocholate (10/31 μM). *Hormones and their conjugates*: DHEAS (8/8 μM), $E_2$17βG (35/45 μM), E-3-S (12/15 μM), T_3 (44/25 μM), T_4 (20/12 μM). *Eicosanoids*: prostaglandine E_2. *Drugs*: methotrexate (1–2 μM), zidovudine (64/76 μM). *Other organic anions*: folate. *Toxins*: ochratoxin A (6/17 μM).	Protein: kidney	[41,50–52]
Oatp2 (*Slc21a5*)	661	*Bile salts*: cholate (46 μM), glycocholate (40 μM), taurocholate (35 μM), TCDCA (12 μM), TUDCA (17 μM). *Hormones and their conjugates*: DHEAS (17 μM), $E_2$17βG (3 μM), E-3-S (11 μM), T_3 (6 μM), T_4 (7 μM). *Peptides*: BQ-123 (30 μM), DPDPE (19 μM), Leu-enkephalin. *Drugs*: biotin, digoxin (240 nM), fexofenadine (6 μM), ouabain (470 μM), pravastatin (38 μM). *Organic cations*: APD-ajmalinium, rocuronium.	mRNA: liver, kidney, brain, retina Protein: liver, BBB, choroid plexus, retina	[28,33,35,39, 40,53–55]
Oatp3 (*Slc21a7*)	670	*Bile salts*: cholate (3 μM), glycocholate (15 μM), glycodeoxycholate (4 μM), GCDCA (6 μM), GUDCA (5 μM), taurocholate (18–30 μM), taurodeoxycholate (6 μM), TCDCA (7 μM), TUDCA (7 μM). *Hormones and their conjugates*: DHEAS (162 μM), $E_2$17βG (39 μM), E-3-S (268 μM), T_3 (7 μM), T_4 (5 μM). *Eicosanoids*: LTC4, prostaglandine E_2 (35 μM). *Peptides*: BQ-123 (417 μM), DPDPE (137 μM). *Drugs*: digoxin, fexofenadine, ouabain (1.6 mM). *Other organic anions*: BSP (8 μM). *Organic cations*: rocuronium.	mRNA: retina, brain, kidney, liver, small intestine Protein: jejunum, choroid plexus (?)	[53,56–58]
Oatp9 (*Slc21a9*)	682	*Bile salts*: taurocholate (18 μM). *Eicosanoids*: LTC_4 (3 μM), prostaglandine D_2 (36 nM), prostaglandine E_1, prostaglandine E_2, thromboxane B_2. *Drugs*: iloprost.	mRNA: liver, lung, heart, brain, retina, kidney	[59]
Oatp4 (*Slc21a10*)	687	*Bile salts*: taurocholate (27 μM). *Hormones and their conjugates*: DHEAS (5 μM), $E_2$17βG (32 μM), E-3-S (37 μM), T_3, T_4. *Eicosanoids*: LTC_4 (7 μM), prostaglandine E_2 (13 μM). *Other organic anions*: BSP (1 μM). *Toxins*: mycrocystin, phalloidin[b].	Protein: liver, eye	[58,60–62]
Oatp11 (*Slc21a11*)	710			
Oatp12 (*Slc21a12*)	722	*Bile salts*: taurocholate. *Hormones*: T_3. *Eicosanoids*: prostaglandine E_2.		[18]

(continued on next page)

Table 3 (*continued*)

Transporter	Size[a]	Substrates (K_m value)	Main location	References
Rat Oatps				
Oatp5 (*Slc21a13*)	670		mRNA: kidney	Genbank: AF053317
Oatp14 (*Slc21a14*)	716		mRNA: brain	[63]
Human OATPs				
hPGT (*SLC21A2*)	643	*Eicosanoids*: prostaglandine D_2, prostaglandine E_1, prostaglandine E_2, prostaglandine $E_{2\alpha}$, thromboxane B_2.	Ubiquitously	[10]
OATP-A (*SLC21A3*)	670	*Bile salts*: cholate (93 μM), glycocholate, taruocholate (60 μM),TCDCA, TUDCA (19 μM). *Hormones and their conjugates*: DHEAS (7 μM), $E_2$17βG, E-3-S (59 μM), T_3 (7 μM), rT_3, T_4 (8 μM). *Eicosanoids*: prostaglandine E_2. *Peptides*: BQ-123, CRC220, deltorphin II (330 μM), DPDPE (202 μM). *Drugs*: chlorambuciltaurocholate, fexofenadine (6 μM), Gd-B 20790, ouabain (5.5 mM). *Other organic anions*: BSP (20 μM). *Organic cations*: APD-ajmalinium, *N*-methylquinine (26 μM), *N*-methylquinidine (5 μM), rocuronium. *Toxins*: microcystin.	mRNA: brain, kidney, liver, lung, testis Protein: brain, liver	[1,5,18,33,35, 39,62,64–68]
OATP-C (*SLC21A6*)	691	*Bile salts*: cholate (11 μM), glycocholate, taurocholate (10–34 μM). *Hormones and their conjugates*: DHEAS (22 μM), $E_2$17βG (8–10 μM), E-3-S (13 μM), T_3 (3 μM), T_4 (3 μM). *Eicosanoids*: LTC_4, LTE_4, prostaglandine E_2, thromboxane B_2. *Peptides*: BQ-123, DPDPE. *Drugs*: benzylpenicillin, methotrexate, pravastatin (14–35 μM), rifampicin (13 μM). *Other organic anions*: bilirubin, monoglucuronosyl bilirubin (100 nM), bisglucuronosyl bilirubin (300 nM), BSP (100–300 nM). *Toxins*: microcystin, phalloidin[b].	Protein: Liver	[4,5,38,62,69–73]
OATP8 (*SLC21A8*)	702	*Bile salts*: glycocholate, taurocholate (6 μM). *Hormones and their conjugates*: DHEAS, $E_2$17βG (5 μM), E-3-S, T_3 (6 μM), T_4. *Eicosanoids*: LTC_4. *Pepdites*: BQ-123, CCK-8 (11 μM), deltorphin II, DPDPE. *Drugs*: digoxin, methotrexate (25 μM), ouabain, rifampicin (2 μM). *Other organic anions*: monoglucuronosyl bilirubin (500 nM), BSP (0.4–3 μM). *Toxins*: microcystin, phalloidin[b].	Protein: liver	[5,61,62,69,72–74]
OATP-B (*SLC21A9*)	709	E-3-S (6 μM), DHEAS, benzylpenicillin, BSP (0.7 μM).	mRNA: liver, placenta, spleen, lung, kidney, heart, ovary, small intestine, brain Protein: liver, placenta	[4,5]
OATP-D (*SLC21A11*)	710	E-3-S, prostaglandine E_2, benzylpenicillin.	Ubiquitously	[4]
OATP-E (*SLC21A12*)	722	Taurocholate (15 μM), E-3-S, $E_2$17βG, T_3 (1 μM), rT_3, T_4, prostaglandine E_2.	Ubiquitously	[4,18]
OATP-F (*SLC21A14*)	712	$E_2$17βG, E-3-S, T_3, rT_3 (130 nM), T_4 (90 nM), BSP.	Protein: brain, testis	[21]

Abbreviations: APD-ajmalinium: *N*-(4,4-azo-*n*-pentyl)-21-deoxyajmalinium; BSP: bromosulfophthalein; BSP-SG: gluthathione-conjugated BSP; DNP-SG: dinitrophenyl-glutathione; CCK8: cholecystokinin-8; DHEAS: dehydroepiandrosterone-sulfate; DAMGO: D-Ala^2,*N*-Me-Phe^4,Gly^5-ol]-Enkephalin; DPDPE: [D-Pen^{2,5}]-Enkephalin; E-3-S: estrone-3-sulfate; $E_2$17βG: estradiol-17β-glucuronide; GCDCA, glycochenodeoxycholate; Gd-B 20790, gadolinium derivative; GUDCA, glycoursodeoxycholate; TCDCA, taurochenodeoxycholate; TUDCA, tauroursodeoxycholate.

[a] Amino acids.

[b] Unpublished own observation.

4.3. Tissue distribution

The tissue distribution of Oatps/OATPs has been studied using different techniques. Consistent with their potential role in detoxification processes, Oatps/OATPs are expressed in various tissues as demonstrated for example by RT-PCR techniques in normal rat [79] and human tissues as well as in human cancer cell lines [4]. Certain transporters show a more restricted tissue expression pattern (e.g. Oatp1, Oatp2, Oatp3, Oatp4, OATP-A, OATP-C, OATP8 and OATP-F)

while others can be detected in almost every tissue that has been investigated (e.g. Oatp9, OATP-B, OATP-D and OATP-E). This indicates that some Oatps/OATPs have organ-specific functions while others might be involved in more housekeeping functions.

4.3.1. Liver

In rat (Oatp1, Oatp2 and Oatp4) and human liver (OATP-B, OATP-C and OATP8) all Oatps/OATPs are expressed at the sinusoidal (basolateral) plasma membrane where they are responsible for uptake and elimination of a wide variety of amphipathic endo- and xenobiotics (Table 3). Rifamycin SV and rifampicin, two structurally related antibiotics that are mainly used in the treatment of tuberculosis, have been shown to induce hyperbilirubinemia and to reduce hepatic elimination of BSP. In recent studies [72,80], the effect of these antibiotics was tested on Oatp/OATP-mediated transport and it could be demonstrated that rifamycin is a potent inhibitor of rat Oatp1 and Oatp2 as well as of all human liver OATPs with K_i values in the low micromolar range while rifampicin mainly inhibits rat Oatp2 and human OATP8 and to a lesser degree also OATP-C [72,80]. These results have important implications for drug development and drug therapy because Oatps/OATPs can play an important role in the hepatic first pass clearance of numerous drugs [27,81]. Therefore, coadministration of a specific OATP-inhibitor could be used to increase the oral bioavailability of drugs that otherwise have a high Oatp/OATP-mediated first pass elimination. On the other hand, induction of Oatp/OATP gene expression (e.g. by rifampicin via the PXR receptor, see below) could increase the first pass elimination of drugs that are less efficient Oatp/OATP substrates and decrease their bioavailability to therapeutically inefficient plasma concentrations. Furthermore, adverse drug reactions such as decreased drug efficacy or even therapeutic failure of an intrahepatically active drug (e.g. pravastatin) could be due to coadministration of an Oatp/OATP inhibitor. Thus, inhibition of liver Oatps/OATPs that transport a wide spectrum of compounds (Table 3) may have important consequences for overall bioavailability and toxicity of xenobiotics and should be considered during drug development.

4.3.2. Brain

Certain drugs have to be transported into and toxic waste products have to be eliminated from the brain. These compounds need to be transported either across the BBB or the blood cerebrospinal fluid barrier. In both epithelial layers, Oatps/OATPs have been identified. At the BBB, rat Oatp2 and human OATP-A are both expressed in endothelial cells where they could mediate efflux of metabolites (e.g glucuronidates, GHS-conjugates or sulfates) [82] and/or uptake of drugs such as opioid peptides [35]. These in vitro predictions were confirmed by in vivo experiments using Mdr1a knockout and wild-type mice where transport of the delta opioid receptor agonist DPDPE was studied using a brain perfusion technique [83]. Due to Mrd1a mediated efflux, DPDPE exhibited poor BBB permeability in wild-type mice while in the Mdr1a knockout mice uptake of DPDPE could readily be determined, suggesting that Oatp2 is responsible for saturable uptake of DPDPE and potentially other opioid peptides across the BBB into the brain. Similarly, the brain level ratio between Mdr1a-deficient and normal mice was elevated for numerous compounds including the high affinity Oatp2 substrate digoxin [84]. In addition, efflux of estradiol-17β-glucuronide across the rat BBB could be mainly inhibited by digoxin, supporting a major role of Oatp2 for estradiol-17β-glucuronide efflux [85].

In the rat choroid plexus epithelium two Oatps have been localized. Oatp2 is expressed at the basolateral membrane [77] while at the apical membrane Oatp1 was identified [86,87]. However, since the antibody used was raised against the C-terminal end and also recognizes Oatp3, it could well be that Oatp3 is expressed in the apical membrane of choroid plexus. Actually, there is additional indirect evidence for Oatp3 expression at the choroid plexus. Using quantitative RT-PCR, mRNA for Oatp3 was readily detected in rat brain while no signal was obtained for Oatp1 [79]. Furthermore, the dichotomous development proposed for Oatp1 in the liver and the choroid plexus, which was examined using the same antibody [88], could be easily explained with the presence of different proteins in liver (Oatp1) and brain (Oatp3). And finally, while in the liver both Oatp1 as well as Oatp2 are expressed in the same basolateral plasma membrane, in the small intestine, Oatp3 is expressed in the apical membrane [57]. Functionally, the two Oatps can account for transepithelial secretion of GSH and efficient removal of LTC_4 from the cerebrospinal fluid [87] but also for transepithelial uptake of thyroid hormones into the brain.

The recently characterized human OATP-F is a high affinity thyroxine and reverse triiodo-thyrosine transporter (Table 3) and is selectively expressed in brain and to a lesser degree also in testis [21] where it may play an important role in the local disposition of iodothyronines. Based on Northern blot analysis, OATP-F is expressed in various brain regions; however, its exact cellular localization remains to be determined.

4.3.3. Kidney

In the kidney several Oatps/OATPs have been identified at the mRNA level (Oatp1, Oatp2, Oatp5, OAT-K1/2, OATP-A, OATP-B, OATP-D and OATP-E); however, at the protein level only Oatp1 [89] and OAT-K1/2 [51,90] have been identified. Using an antibody against the C-terminal end, which also recognizes Oatp3 (see above), Oatp1 was identified at the apical plasma membrane in the S3 segment of the proximal tubule [89]. Quantitative RT-PCR results confirmed the presence of Oatp1 in renal RNA while OATP3 was not detected [79]. Functionally, Oatp1 could be responsible for reabsorption of organic

compounds that are freely filtered, such as estradiol-17β-glucuronide (see also below) [91], or important for the secretion of certain organic compounds that are taken up into proximal tubular cells across the basolateral membrane.

OAT-K1 is selectively expressed at the apical plasma membrane of proximal tubular epithelial cells [90]. As a high affinity methotrexate transporter, it could be involved in the urinary secretion of this drug and thus protect renal cells [52]. Together with a splice variant, OAT-K2, which is also exclusively expressed in the kidney, these multispecific organic anion transporters seem to contribute to the renal secretion and/or reabsorption of hydrophobic anionic compounds [51]. Interestingly, these two proteins are so far specific for the rat since no orthologues have been identified in mice.

Oatp5 is another kidney-specific Oatp since its mRNA has not been detected in any other tissue [79]. Unfortunately, so far no functional data are available and the physiological role of Oatp5 is still unknown.

4.3.4. Placenta

Bile acids that are synthesized in utero by the fetal liver are transported across the trophoblast epithelium from the fetal to the maternal circulation. On a functional level, bile salt uptake across the basolateral (fetal facing) membrane is Na^+-independent and thus could be Oatp/OATP-mediated [19]. Furthermore, during pregnancy the placenta is a major source of steroid hormones that are transported as sulfate conjugates (e.g. dehydroepiandrosterone-sulfate (DHEAS), pregnenolone sulfate). These sulfate conjugates are organic anions and thus (potential) substrates of several Oatps/OATPs [20]. At the RNA level, several Oatps/OATPs have been localized to the placenta including Oatp9 and Oatp12 in the rat [92], and OATP-B, OATP-D and OATP-E in man [4]. At the protein level, so far only OATP-B has been detected in the trophoblast at the basal membranes where it may play a role in transporting natural substrates (e.g. steroid hormone conjugates) from the fetal circulation into the trophoblast [20]. However, since OATP-B has a narrow substrate specificity and does not transport bile salts [5], additional (not yet identified) transport systems are probably responsible for the elimination of bile acids and other organic anions from the fetal circulation.

4.3.5. Eye

Rat Oatp2 and Oatp3 have been cloned, besides from brain [40] and intestine [57], also from a retina cDNA library [53]. Recently, using a specific antibody, Oatp2 could be localized to the retinal pigment epithelium, which plays a vital role in the maintenance and function of photoreceptors [93]. Oatp2 is expressed in the apical membrane of this epithelium where it could be involved in the transport of retinoids into and out of retinal pigment epithelial cells.

The ciliary epithelium with its pigmented and non-pigmented cell layers forms the barrier between the eye (aqueous humor) and the rest of the body (blood) similar to the BBB. Multispecific organic anion transport systems have been suggested to be present in this epithelium for a long time and indeed, preliminary data from our lab indicate that several Oatps/OATPs are expressed in the nonpigmented ciliary epithelium of the rat (Oatp2 and Oatp4) and the human eye (OATP-A, OATP-B, OATP-D and OATP-E) (Gao and Meier, unpublished) where they might be involved in maintaining the homeostasis of the aqueous humor.

5. Regulation of Oatps/OATPs

5.1. Ontogenic expression

Several groups have studied ontogenic expression of Oatps/OATPs in developing rat liver. In contrast to the major bile salt transporters Ntcp and the bile salt export pump Bsep, which were expressed around birth, significant expression of Oatp1, Oatp2 and Oatp4 could only be detected on the protein level during the first four weeks after birth [94]. Similar results were also obtained on the mRNA levels for rat liver Oatp2 and Oatp4 [79,95]. In contrast, in the choroid plexus Oatp1 was detected already at birth [88]. However, since the antibody used also recognizes Oatp3, it cannot be excluded that the obtained signal was actually due to Oatp3 expression (see above). Using real-time PCR, several Oatps could be detected at very low levels during late pregnancy. At birth, the expression levels increased to 15% of adult levels for Oatp1, to 0.05% for Oatp2, to 30% for Oatp4 and to 20% for Oatp9 [92]. Based on Northern blot analysis, Oatp5 expression in the kidney was similarly to Oatp expression in the liver detected only late during development and could not be seen during the first 3 weeks after birth [96]. Hence, in general, Oatps are expressed rather late during rat liver development, indicating that they play no major role in the development of the enterohepatic circulation of bile salts.

5.2. Gender differences

Regulation of Oatp1 expression and function occurs at transcriptional and post-transcriptional levels and is, at least in part, tissue-specific. Thus, while in the kidney Oatp1 expression is stimulated by testosterone and inhibited by estrogens, hepatic Oatp1 expression is not influenced by sex hormones [91,97,98]. As a consequence, kidney Oatp1 is considerably less abundantly expressed in female as compared to male rats [98]. This gender difference in the renal expression of apical Oatp1 is associated with increased urinary excretion of estradiol-17β-D-glucuronide in female as compared to male rats [91]. Whether expression of other Oatps/OATPs is also affected by sex hormones remains to be determined.

5.3. Transcriptional regulation

Transcriptional regulation has so far been studied for only a few Oatps/OATPs. In the rat, *Oatp2* gene expression is induced by phenobarbital [99] and pregnenolone-16α-carbonitrile (PCN), a well-known inducer of cytochrome P450 enzymes of the 3A family [100,101]. The mechanism of PCN induction has been investigated in detail and several pregnane X receptor (PXR) response elements have been identified on the rat Oatp2 promoter [102]. Since lithocholic acid, a cholestatic secondary bile acid formed in the intestine by bacterial 7α-dehydroxylation of chenodeoxycholic acid, is an endogenous ligand of PXR, concomitant PXR-dependent up-regulation of Oatp2 (uptake) and CYP3A (hydroxylation) represents an important constitutive response in the hepatic detoxification of both cholestatic bile salts and xenobiotic chemicals [101,103]. Hepatic expression of the human OATP-C gene has been shown to be dependent on the liver-enriched transcription factor HNF-1α [104]. Similarly, hepatic OATP8 expression is dependent on HNF-1α [104] but, in addition, can be influenced by the bile acid nuclear receptor FXR/BAR [105]. Whether human liver OATPs can also be regulated by the xenobiotic receptor PXR remains to be investigated.

5.4. Post-transcriptional regulation

On the protein level, functional regulation of Oatps has been demonstrated for rat Oatp1 and Oatp2 [106,107]. Functional down-regulation of Oatp1 can occur via serine phosphorylation by extracellular ATP [106]. In addition, protein kinase C activation leads to decreased transport of estrone-3-sulfate in Oatp1 expressing *X. laevis* oocytes [107]. Hence, phosphorylated Oatp1 can lose its transport activity without leaving the cell surface, indicating that the phosphorylation state of membrane-associated Oatp1 must be considered when assessing its functional alterations in pathological states. Similarly, protein kinase C activators suppress Oatp2-mediated digoxin transport in *X. laevis* oocytes, demonstrating that also Oatp2 is regulated at the protein level [107].

6. Expression and function in disease and disease models

So far no Oatp knockout mice have been generated. However, Oatp expression has been investigated in several knockout mouse models such as the HNF-1α- [108] and HNF4α- [109] deficient mice, where all tested liver Oatps are down-regulated, suggesting further an important role for these two transcription factors in basal Oatp expression in the liver. Furthermore, in mice with disrupted bile acid receptor FXR/BAR, cholate feeding was associated with increased Oatp1 expression [110]. Whether this negative feedback regulation of Oatp1 by FXR/BAR occurs via inhibition of the retinoid X receptor (RXR) and retinoic acid receptor (RAR) heterodimer RXR:RAR or by the FXR/BAR-dependent small heterodimer partner 1 (SHP-1) [111] is not yet known. In PXR-deficient mice, basal Oatp2 expression was not changed but could not be induced anymore by PCN (see above [101]).

Although several polymorphisms that affect substrate transport mediated by the human OATP-C and OATP-B have been identified [112,113], so far no evidence exists that impaired Oatp/OATP function would cause a known disease. However, in several models of cholestatic liver diseases such as endotoxin treatment (for sepsis-induced cholestasis), ethinyl estradiol treatment (for cholestasis of pregnancy) and bile duct ligation (for extrahepatic biliary obstructions), expression of hepatocellular Oatps was down-regulated [3,114]. Furthermore, cholate feeding of mice resulted in down-regulation of Oatp1 mRNA expression by about 25% and protein expression by 90%. Oatp4 mRNA expression was down-regulated by 55% [115]. Following partial hepatectomy, expression of rat Oatp1 declined rapidly to about 50% within 2 days and recovered to normal levels at 4 days, while Oatp2 was maximally down-regulated between days 4 and 7 and returned to almost normal levels by 14 days [116]. In an animal model of primary sclerosing cholangitis (PSC), Oatp1 and Oatp2 protein levels were 22% and 21% of controls, respectively, while Oatp4 remained unchanged [117]. Similarly, in patients with PSC, OATP-C mRNA levels are decreased to ~50% as compared to control livers [118]. Hence, during cholestasis and massive liver regeneration, down-regulation of basolateral expression of hepatocellular Oatps provides an explanation, at least in part, for the functional transport defects associated with these pathological conditions.

7. Suggestion for new classification and nomenclature

As repeatedly indicated in the previous sections, the rapid independent identification of new Oatps/OATPs has led to a proliferation of different names for identical proteins (see Table 1). Since membrane transporters are generally named according to their function, and since polytopic expression of any Oatp/OATP in various organs cannot be excluded until all tissues of the body will have been examined, an organ specific nomenclature such as "liver specific transporter (LST)" should be avoided as illustrated with LST-2, which is also abundantly expressed in cancers of several organs [73] and thus is not a liver specific transporter. Furthermore, the human OATP2 has only a 46% amino acid sequence identity to the previously cloned rat Oatp2 (Table 2), and therefore the two proteins do not represent orthologous gene products. True orthologous gene products have so far been identified in OATP families 2, 3 and 4 (Fig. 4). In order to avoid false associations of non-orthologous gene products between species and to avoid confusion in the future scientific discussions, clearly defined

distinct names should be given to different gene products. In this regard the provisional alphabetic ordering of the human OATPs (i.e. OATP-A, OATP-B, OATP-C, etc.) is advantageous, since it does not overlap with the previously established continuous numbering of non-orthologous rat Oatps. However, an alphabetic gene nomenclature is unusual since the general rule is the continuous and species independent numbering of orthologous gene products. Therefore, alphabetic ordering of human OATPs can only provisionally be used until sequencing of the human, mouse and rat genomes will have been completed and all Oatp/OATP orthologous genes will have been identified in these species.

The so far used classification system, based on the rules of the human and mouse/rat gene nomenclature committees (SLC21A/Slc21a), unfortunately does not permit an unequivocal and species independent identification of the various *Oatp*/*OATP* genes. It neither allows the sub-classification of individual transporter superfamilies according to the well-established rules of, for example, the cytochrome P450 superfamily system [16] since it treats all solute carriers as only one superfamily. Therefore, a classification and nomenclature system is required that is based on divergent evolution and defines an OATP superfamily that is divided into families, subfamilies and individual gene products according to the degree of amino acid sequence identities and evolutionary relationships. Such a system has been proven to be extremely helpful and convenient for the classification of the cytochrome P450 and other drug-metabolizing enzyme superfamilies [14–16], and could be implemented easily also for the Oatps/OATPs and possibly other polyspecific transporter families. It could well replace the current SLC-classification once sequencing of the human, mouse and rat genomes will have been completed.

The wide variation of the Oatp/OATP amino acid sequence identities (Table 2) results in a clear clustering of the individual proteins into families and subfamilies as is visualized using a phylogenetic tree (Fig. 4). Following the guidelines of the nomenclature committees of the drug-metabolizing enzymes [14–16], we therefore classified the various Oatps/OATPs into different gene families with less than 40% amino acid sequence identities to members of any other family and named them OATP1, OATP2, OATP3, OATP4 and OATP5 (see above and Fig. 4). Oatps/OATPs within the same family share more than 40% amino acid sequence identities among each other (Table 2, Fig. 4). Individual subfamilies include Oatps/OATPs with amino acid sequence identities of more than 60% and are designated with letters (e.g. OATP1A, OATP1B etc.; Fig. 4). If

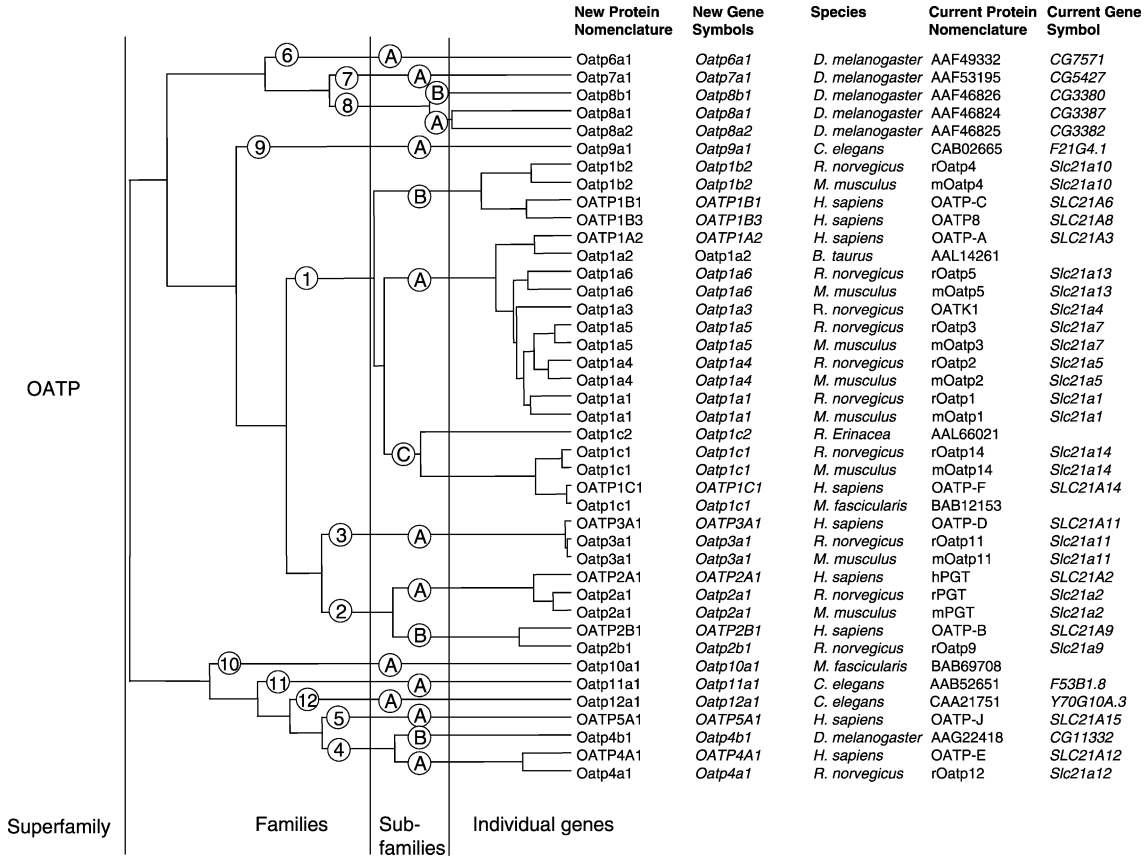

Fig. 5. Classification and suggested new nomenclature of 41 members of the OATP gene superfamily. Individual genes are categorized into families and subfamilies based on their amino acid sequence identities of 40–60% and ≥60%, respectively. The phylogram was calculated using the GCG programs PILEUP, DISTANCES and GROWTREE and visualized using the program TreeView [17]. Where available the current gene symbols are given. The "Current Nomenclature" column lists the currently used names of the known Oatp/OATPs and the protein accession number for the other proteins.

there are several individual genes within the same subfamily, additional continuous Arabic numbering based on the chronology of gene identification can be used. Following these rules, the OATP superfamily can presently be divided into 12 families with a total number of 41 genes. In addition, screening the EST databases, we identified related protein fragments (amino acid identities 43–98%) from numerous species including, e.g. sea urchin (*Strongylocentrotus purpuratus*), sea squirt (*Ciona intestinalis*), honey bee (*Apis mellifera*), zebrafish (*Danio rerio*), catfish (*Ictalulurs punctatus*), frogs (*Xenopus laevis* and *Silurana tropicalis*), chicken (*Gallus gallus*) and pig (*Sus scorfa*). They were not yet included because they do not encode full-length proteins. However, this emphasizes again the need for the suggested new classification and nomenclature system, illustrated in Fig. 5, which can identify unambiguously all present and future members of the superfamily by assigning (1) the superfamily designation OATP (human members) or Oatp (animal species), (2) the family number, (3) the subfamily letter (capital letters for human members, small letters for animal members), and (4) continuous Arabic numbering according to the chronology of gene identification. We suggest that the phylogenetically based new classification and nomenclature system should replace the chaotic and partially erroneous current nomenclature (Table 1, Fig. 5) in the near future, since this suggested new classification and nomenclature system takes into account the molecular and phylogenetic relationships between individual genes, allows to differentiate between orthologous human and rodent proteins (OATP1A as compared to Oatp1a), is easy to follow, and provides an unambiguous open-ended nomenclature for all members of the OATP superfamily.

8. Conclusions and perspectives

There are currently 31 mammalian members of the OATP superfamily. Many of these proteins are multispecific and transport a broad range of amphipathic endo- and xenobiotics. Their expression in multiple tissues including the liver, the kidney, the small intestine and the BBB puts them into a strategic position for absorption, distribution and excretion of drugs and toxins. Thus, Oatps/OATPs are important transporters of the overall body detoxification system. Furthermore, the predominant or even exclusive localization of certain Oatps/OATPs in some tissues (e.g. "liver-specific" Oatp4, OATP-C and OATP8; restricted expression of OATP-F in brain and testis) indicates that selective transporters might be suitable for tissue-specific drug targeting.

The OATP superfamily is rapidly growing since new members continue to be discovered through genome-wide sequencing projects such as the "Fugu Genome Project". Further members are expected to be identified during genomic sequencing of additional species including cat, dog and bovine genomes.

Besides the members of the OATP superfamily, there are additional organic anion transporters (OATs) and OCTs that are classified within the solute carrier family 22A [42,43]. These transporters are predominantly expressed in the kidney (basolateral membrane of proximal tubular epithelial cells) where they are involved in the renal excretion of small hydrophilic organic anions (OATs) and organic cations (OCTs). Although a few typical Oatp/OATP compounds are also substrates of certain OATs (e.g. estrone-3-sulfate, ochratoxin A) and OCTs (e.g. *N*-methyl-quinidine), the distinct substrate preferences of Oatps/OATPs and OATs/OCTs complement each other. Thus, while Oatps/OATPs can account for the hepatic clearance of larger amphipathic albumin-bound organic compounds, OATs/OCTs are responsible for active renal excretion of small hydrophilic organic substances. Hence, Oatps/OATPs and OATs/OCTs represent important drug carriers with complementary transport functions that have to be taken into account for rational drug design and targeting.

Although rapid progress has been made in the identification of individual members of the OATP superfamily, numerous questions remain unanswered and require more detailed investigations in the near future. They relate especially to (1) the elucidation of the exact tissue expression of individual Oatps/OATPs under physiologic and various pathophysiologic (disease dependent altered expression?) conditions, (2) the more detailed characterization of the driving force(s) involved in Oatp/OATP-mediated substrate transport, (3) a more detailed understanding of the molecular basis of the broad substrate specificity of most Oatps/OATPs through detailed structure/function, site-directed mutagenesis and crystallization studies in isolated proteins, (4) the development of specific inhibitors for individual Oatps/OATPs, (5) investigation of the transcriptional and post-transcriptional regulation of individual transporter expression, (6) elucidation of functionally important interactions of Oatps/OATPs with cytosolic and other membrane proteins, (7) identification of gene polymorphisms and elucidation of their functional consequences for overall drug absorption and disposition (genotype/phenotype correlation), and (8) elucidation of the overall significance of individual Oatps/OATPs for physiology and pathophysiology through generation of gene knock-out models in cases where true Oatp/OATP homologues have been identified and/or the use of model organisms such as *C. elegans* and *D. melanogaster*.

Obviously a standardized and unified nomenclature system is an urgent requirement to perform successfully the abovementioned future studies and to avoid further misunderstandings between various research groups. The urgency of this step is underlined by several recent examples of erroneous assignments of functional properties of rat Oatp2 to human OATP2 (OATP-C) [6] and of rat Oatp2 to OAT2 [119]. Furthermore, an organ-specific nomenclature has been used for newly identified Oatps/OATPs despite the fact that the respective transporter is also expressed in other

tissues [73] and/or probably represents a true orthologue of a multilocalized transporter in another species (e.g. ≥80% amino acid identities between the bovine "liver-specific organic anion transporter" (accession number AY052775) and human OATP-A). In order to avoid further confusions and to help young investigators in the field, we propose the implementation of a new phylogenetically based, species independent and unambiguous open-ended nomenclature for all members of the OATP superfamily that has been adapted from the successful classification system of the cytochrome P450 superfamily (see Fig. 5). Our proposed new classification and nomenclature system for the OATP superfamily is in full agreement with the recent nomenclature guidelines of the Human Nomenclature Committee [120].

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References

[1] P.J. Meier, U. Eckhardt, A. Schroeder, B. Hagenbuch, B. Stieger, Hepatology 26 (1997) 1667–1677.
[2] G.A. Kullak-Ublick, B. Stieger, B. Hagenbuch, P.J. Meier, Semin. Liver Dis. 20 (2000) 273–292.
[3] P.J. Meier, B. Stieger, Annu. Rev. Physiol. 64 (2002) 635–661.
[4] I. Tamai, J. Nezu, H. Uchino, Y. Sai, A. Oku, M. Shimane, A. Tsuji, Biochem. Biophys. Res. Commun. 273 (2000) 251–260.
[5] G.A. Kullak-Ublick, M.G. Ismair, B. Stieger, L. Landmann, R. Huber, F. Pizzagalli, K. Fattinger, P.J. Meier, B. Hagenbuch, Gastroenterology 120 (2001) 525–533.
[6] P.L.M. Jansen, M. Müller, Hepatology 34 (2001) 1067–1074.
[7] E. Jacquemin, B. Hagenbuch, B. Stieger, A.W. Wolkoff, P.J. Meier, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 133–137.
[8] D.J. Hakes, R. Berezney, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 6186–6190.
[9] P.J. Wang, S. Hata, A.W. Wolkoff, Hepatology 30 (1999) 584A.
[10] R. Lu, N. Kanai, Y. Bao, V.L. Schuster, J. Clin. Invest. 98 (1996) 1142–1149.
[11] N. Kanai, R. Lu, J.A. Satriano, Y. Bao, A.W. Wolkoff, V.L. Schuster, Science 268 (1995) 866–869.
[12] J. Devereux, P. Haeberli, O. Smithies, Nucleic Acids Res. 12 (1984) 387–395.
[13] A. Krogh, B. Larsson, G. von Heijne, E.L.L. Sonnhammer, J. Mol. Biol. 305 (2001) 567–580.
[14] V. Vasiliou, A. Bairoch, K.F. Tipton, D.W. Nebert, Pharmacogenetics 9 (1999) 421–434.
[15] P.I. Mackenzie, I.S. Owens, B. Burchell, K.W. Bock, A. Bairoch, A. Bélanger, S. Fournel-Gigleux, M. Green, D.W. Hum, T. Iyanagi, D. Lancet, P. Louisot, J. Magdalou, J. Roy Chowdhury, J.K. Ritter, H. Schachter, T.R. Tephly, K.F. Tipton, D.W. Nebert, Pharmacogenetics 7 (1997) 255–269.
[16] D.R. Nelson, L. Koymans, T. Kamataki, J.J. Stegeman, R. Feyereisen, D.J. Waxman, M.R. Waterman, O. Gotoh, M.J. Coon, R.W. Estabrook, I.C. Gunsalus, D.W. Nebert, Pharmacogenetics 6 (1996) 1–42.
[17] R.D.M. Page, Comput. Appl. Biosci. 12 (1996) 357–358.
[18] K. Fujiwara, H. Adachi, T. Nishio, M. Unno, T. Tokui, M. Okabe, T. Onogawa, T. Suzuki, N. Asano, M. Tanemoto, M. Seki, K. Shiiba, M. Suzuki, Y. Kondo, K. Nunoki, T. Shimosegawa, K. Iinuma, S. Ito, S. Matsuno, T. Abe, Endocrinology 142 (2001) 2005–2012.
[19] M.V. St-Pierre, G.A. Kullak-Ublick, B. Hagenbuch, P.J. Meier, J. Exp. Biol. 204 (2001) 1673–1686.
[20] M.V. St-Pierre, B. Ugele, B. Hagenbuch, P.J. Meier, T. Stallmach, J. Clin. Endocrinol. Metab. 87 (2002) 1856–1863.
[21] F. Pizzagalli, B. Hagenbuch, B. Stieger, U. Klenk, G. Folkers, P.J. Meier, Mol. Endocrinol. 16 (2002) 2283–2296.
[22] S.-Y. Cai, W. Wang, C.J. Soroka, N. Ballatori, J.L. Boyer, Hepatology 34 (2001) A1208.
[23] B. Hagenbuch, I.-D. Adler, T.E. Schmid, Biochem. J. 345 (2000) 115–120.
[24] E. Jacquemin, B. Hagenbuch, B. Stieger, A.W. Wolkoff, P.J. Meier, J. Clin. Invest. 88 (1991) 2146–2149.
[25] X.Y. Shi, S. Bai, A.C. Ford, R.D. Burk, E. Jacquemin, B. Hagenbuch, P.J. Meier, A.W. Wolkoff, J. Biol. Chem. 270 (1995) 25591–25595.
[26] G.-A. Kullak-Ublick, B. Hagenbuch, B. Stieger, A.W. Wolkoff, P.J. Meier, Hepatology 20 (1994) 411–416.
[27] U. Eckhardt, A. Schroeder, B. Stieger, M. Höchli, L. Landmann, R. Tynes, P.J. Meier, B. Hagenbuch, Am. J. Physiol. 276 (1999) G1037–G1042.
[28] C. Reichel, B. Gao, J. van Montfoort, V. Cattori, C. Rahner, B. Hagenbuch, B. Stieger, T. Kamisako, P.J. Meier, Gastroenterology 117 (1999) 688–695.
[29] X. Bossuyt, M. Muller, B. Hagenbuch, P.J. Meier, J. Pharmacol. Exp. Ther. 276 (1996) 891–896.
[30] N. Kanai, R. Lu, Y. Bao, A.W. Wolkoff, V.L. Schuster, Am. J. Physiol. 270 (1996) F319–F325.
[31] N. Kanai, R. Lu, Y. Bao, A.W. Wolkoff, M. Vore, V.L. Schuster, Am. J. Physiol. 270 (1996) F326–F331.
[32] E.C. Friesema, R. Docter, E.P. Moerings, B. Stieger, B. Hagenbuch, P.J. Meier, E.P. Krenning, G. Hennemann, T.J. Visser, Biochem. Biophys. Res. Commun. 254 (1999) 497–501.
[33] J.E. van Montfoort, B. Hagenbuch, K. Fattinger, M. Müller, G.M.M. Groothuis, D.K.F. Meijer, P.J. Meier, J. Pharmacol. Exp. Ther. 291 (1999) 147–152.
[34] U. Eckhardt, J.A. Horz, E. Petzinger, W. Stuber, M. Reers, G. Dickneite, H. Daniel, M. Wagener, B. Hagenbuch, B. Stieger, P.J. Meier, Hepatology 24 (1996) 380–384.
[35] B. Gao, B. Hagenbuch, G.A. Kullak-Ublick, D. Benke, A. Aguzzi, P.J. Meier, J. Pharmacol. Exp. Ther. 294 (2000) 73–79.
[36] H. Ishizuka, K. Konno, H. Naganuma, K. Nishimura, H. Kouzuki, H. Suzuki, B. Stieger, P.J. Meier, Y. Sugiyama, J. Pharmacol. Exp. Ther. 287 (1998) 37–42.
[37] K.S. Pang, P.J. Wang, A. Chung, A.W. Wolkoff, Hepatology 28 (1998) 1341–1346.
[38] B. Hsiang, Y. Zhu, Z. Wang, Y. Wu, V. Sasseville, W.-P. Yang, T.G. Kirchgessner, J. Biol. Chem. 274 (1999) 37161–37168.
[39] M. Cvetkovic, B. Leake, M.F. Fromm, G.R. Wilkinson, R.B. Kim, Drug Metab. Dispos. 27 (1999) 866–871.
[40] B. Noé, B. Hagenbuch, B. Stieger, P.J. Meier, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 10346–10350.
[41] H. Saito, S. Masuda, K. Inui, J. Biol. Chem. 271 (1996) 20719–20725.
[42] G. Burckhardt, N.A. Wolff, Am. J. Physiol. 278 (2000) F853–F866.
[43] H. Koepsell, Annu. Rev. Physiol. 60 (1998) 243–266.
[44] L.M. Satlin, V. Amin, A.W. Wolkoff, J. Biol. Chem. 272 (1997) 26340–26345.
[45] L.Q. Li, T.K. Lee, P.J. Meier, N. Ballatori, J. Biol. Chem. 273 (1998) 16184–16191.
[46] H. Kouzuki, H. Suzuki, K. Ito, R. Ohashi, Y. Sugiyama, J. Pharmacol. Exp. Ther. 288 (1999) 627–634.
[47] H. Kouzuki, H. Suzuki, K. Ito, R. Ohashi, Y. Sugiyama, J. Pharmacol. Exp. Ther. 286 (1998) 1043–1050.
[48] J.E. van Montfoort, B. Stieger, D.K. Meijer, H.J. Weinmann, P.J. Meier, K.E. Fattinger, J. Pharmacol. Exp. Ther. 290 (1999) 153–157.

[49] M. Kontaxi, U. Eckhardt, B. Hagenbuch, B. Stieger, P.J. Meier, E. Petzinger, J. Pharmacol. Exp. Ther. 279 (1996) 1507–1513.
[50] A. Takeuchi, S. Masuda, H. Saito, T. Abe, K.-I. Inui, J. Pharmacol. Exp. Ther. 299 (2001) 261–267.
[51] S. Masuda, K. Ibaramoto, A. Takeuchi, H. Saito, Y. Hashimoto, K. Inui, Mol. Pharmacol. 55 (1999) 743–752.
[52] S. Masuda, A. Takeuchi, H. Saito, Y. Hashimoto, K. Inui, FEBS Lett. 459 (1999) 128–132.
[53] T. Abe, M. Kakyo, H. Sakagami, T. Tokui, T. Nishio, M. Tanemoto, H. Nomura, S.C. Hebert, S. Masuno, H. Kondo, H. Yawo, J. Biol. Chem. 273 (1998) 22395–22401.
[54] M. Kakyo, H. Sakagami, T. Nishio, D. Nakai, R. Nakagomi, T. Tokui, T. Naitoh, S. Matsuno, T. Abe, H. Yawo, FEBS Lett. 445 (1999) 343–346.
[55] T. Tokui, D. Nakai, R. Nakagomi, H. Yawo, T. Abe, Y. Sugiyama, Pharm. Res. 16 (1999) 904–908.
[56] G.K. Dresser, D.G. Bailey, B.F. Leake, U.I. Schwarz, P.A. Dawson, D.J. Freeman, R.B. Kim, Clin. Pharmacol. Ther. 71 (2002) 11–20.
[57] H.C. Walters, A.L. Craddock, H. Fusegawa, M.C. Willingham, P.A. Dawson, Am. J. Physiol. 279 (2000) G1188–G1200.
[58] V. Cattori, J.E. van Montfoort, B. Stieger, L. Landmann, D.K.F. Meijer, K.E. Winterhalter, P.J. Meier, B. Hagenbuch, Pflügers Arch. 443 (2001) 188–195.
[59] T. Nishio, H. Adachi, R. Nakagomi, T. Tokui, E. Sato, M. Tanemoto, K. Fujiwara, M. Okabe, T. Onogawa, T. Suzuki, D. Nakai, K. Shiiba, M. Suzuki, H. Ohtani, Y. Kondo, M. Unno, S. Ito, K. Iinuma, K. Nunoki, S. Matsuno, T. Abe, Biochem. Biophys. Res. Commun. 275 (2000) 831–838.
[60] V. Cattori, B. Hagenbuch, N. Hagenbuch, B. Stieger, R. Ha, K.E. Winterhalter, P.J. Meier, FEBS Lett. 474 (2000) 242–245.
[61] M.G. Ismair, B. Stieger, V. Cattori, B. Hagenbuch, M. Fried, P.J. Meier, G.A. Kullak-Ublick, Gastroenterology 121 (2001) 1185–1190.
[62] W.J. Fischer, J.E. van Montfoort, V. Cattori, P.J. Meier, D.R. Dietrich, B. Hagenbuch, J. Toxicol., Clin. Toxicol. 39 (2001) A565.
[63] J.Y. Li, R.J. Boado, W.M. Pardridge, J. Cereb. Blood Flow Metab. 21 (2001) 61–68.
[64] G.A. Kullak-Ublick, B. Hagenbuch, B. Stieger, C.D. Schteingart, A.F. Hofmann, A.W. Wolkoff, P.J. Meier, Gastroenterology 109 (1995) 1274–1282.
[65] G.A. Kullak-Ublick, J. Glasa, C. Boker, M. Oswald, U. Grutzner, B. Hagenbuch, B. Stieger, P.J. Meier, U. Beuers, W. Kramer, G. Wess, G. Paumgartner, Gastroenterology 113 (1997) 1295–1305.
[66] G.A. Kullak-Ublick, T. Fisch, M. Oswald, B. Hagenbuch, P.J. Meier, U. Beuers, G. Paumgartner, FEBS Lett. 424 (1998) 173–176.
[67] X. Bossuyt, M. Muller, P.J. Meier, J. Hepatol. 25 (1996) 733–738.
[68] L. Pascolo, F. Cupelli, P.L. Anelli, V. Lorusso, M. Visigalli, F. Uggeri, C. Tiribelli, Biochem. Biophys. Res. Commun. 257 (1999) 746–752.
[69] Y. Cui, J. König, I. Leier, U. Buchholz, D. Keppler, J. Biol. Chem. 276 (2001) 9626–9630.
[70] T. Abe, M. Kakyo, T. Tokui, R. Nakagomi, T. Nishio, D. Nakai, H. Nomura, M. Unno, M. Suzuki, T. Naitoh, S. Matsuno, H. Yawo, J. Biol. Chem. 274 (1999) 17159–17163.
[71] D. Nakai, R. Nakagomi, Y. Furuta, T. Tokui, T. Abe, T. Ikeda, K. Nishimura, J. Pharmacol. Exp. Ther. 297 (2001) 861–867.
[72] S.R. Vavricka, J. van Montfoort, H.R. Ha, P.J. Meier, K. Fattinger, Hepatology 36 (2002) 164–172.
[73] T. Abe, M. Unno, T. Onogawa, T. Tokui, T.N. Kondo, R. Nakagomi, H. Adachi, K. Fujiwara, M. Okabe, T. Suzuki, K. Nunoki, E. Sato, M. Kakyo, T. Nishio, J. Sugita, N. Asano, M. Tanemoto, M. Seki, F. Date, K. Ono, Y. Kondo, K. Shiiba, M. Suzuki, H. Ohtani, T. Shimosegawa, K. Iinuma, H. Nagura, S. Ito, S. Matsuno, Gastroenterology 120 (2001) 1689–1699.
[74] J. König, Y. Cui, A.T. Nies, D. Keppler, J. Biol. Chem. 275 (2000) 23161–23168.
[75] B. Hagenbuch, B. Stieger, M. Foguet, H. Lübbert, P.J. Meier, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 10629–10633.
[76] B. Hagenbuch, P.J. Meier, J. Clin. Invest. 93 (1994) 1326–1331.
[77] B. Gao, B. Stieger, B. Noè, J.-M. Fritschy, P.J. Meier, J. Histochem. Cytochem. 47 (1999) 1255–1264.
[78] L. Li, P.J. Meier, N. Ballatori, Mol. Pharmacol. 58 (2000) 335–340.
[79] N. Li, D.P. Hartley, N.J. Cherrington, C.D. Klaassen, J. Pharmacol. Exp. Ther. 301 (2002) 551–560.
[80] K. Fattinger, V. Cattori, B. Hagenbuch, P.J. Meier, B. Stieger, Hepatology 32 (2000) 82–86.
[81] U. Eckhardt, W. Stuber, G. Dickneite, M. Reers, E. Petzinger, Biochem. Pharmacol. 52 (1996) 85–96.
[82] D. Sugiyama, H. Kusuhara, Y. Shitara, T. Abe, P.J. Meier, T. Sekine, H. Endou, H. Suzuki, Y. Sugiyama, J. Pharmacol. Exp. Ther. 298 (2001) 316–322.
[83] C. Dagenais, J. Ducharme, G.M. Pollack, Neurosci. Lett. 301 (2001) 155–158.
[84] A.H. Schinkel, E. Wagenaar, L. van Deemter, C.A.A.M. Mol, P. Borst, J. Clin. Invest. 96 (1995) 1698–1705.
[85] D. Sugiyama, H. Kusuhara, Y. Shitara, T. Abe, Y. Sugiyama, Drug Metab. Dispos. 30 (2002) 220–223.
[86] R.H. Angeletti, P.M. Novikoff, S.R. Juvvadi, J.M. Fritschy, P.J. Meier, A.W. Wolkoff, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 283–286.
[87] B. Gao, P.J. Meier, Microsc. Res. Tech. 52 (2001) 60–64.
[88] R.H. Angeletti, A.J. Bergwerk, P.M. Novikoff, A.W. Wolkoff, Am. J. Physiol. 44 (1998) C882–C887.
[89] A.J. Bergwerk, X.Y. Shi, A.C. Ford, N. Kanai, E. Jacquemin, R.D. Burk, S. Bai, P.M. Novikoff, B. Stieger, P.J. Meier, V.L. Schuster, A.W. Wolkoff, Am. J. Physiol. 271 (1996) G231–G238.
[90] S. Masuda, H. Saito, H. Nonoguchi, K. Tomita, K. Inui, FEBS Lett. 407 (1997) 127–131.
[91] Y. Gotoh, Y. Kato, B. Stieger, P.J. Meier, Y. Sugiyama, Am. J. Physiol. 282 (2002) E1245–E1254.
[92] M.V. St-Pierre, J.-F. Dufour, M.A. Serrano, J.J.G. Marin, P.J. Meier, J. Pharmacol. Exp. Ther. (in press).
[93] B. Gao, A. Wenzel, C. Grimm, S.R. Vavricka, D. Benke, P.J. Meier, C.E. Remè, Investig. Ophthalmol. Vis. Sci. 43 (2002) 510–514.
[94] B. Gao, P.J. Meier, J. Hepatol. 34 (2001) A1200.
[95] G.L. Guo, D.R. Johnson, C.D. Klaassen, Drug Metab. Dispos. 30 (2002) 283–288.
[96] S. Choudhuri, K. Ogura, C.D. Klaassen, Biochem. Biophys. Res. Commun. 280 (2001) 92–98.
[97] R. Lu, N. Kanai, Y. Bao, A.W. Wolkoff, V.L. Schuster, Am. J. Physiol. 39 (1996) F332–F337.
[98] F.R. Simon, J. Fortune, M. Iwahashi, S. Bowman, A. Wolkoff, E. Sutherland, Am. J. Physiol. 276 (1999) G556–G565.
[99] N. Hagenbuch, C. Reichel, B. Stieger, V. Cattori, K.E. Fattinger, L. Landmann, P.J. Meier, G.A. Kullak-Ublick, J. Hepatol. 34 (2001) 881–887.
[100] L.C. Rausch-Derra, D.P. Hartley, P.J. Meier, C.D. Klaassen, Hepatology 33 (2001) 1469–1478.
[101] J.L. Staudinger, B. Goodwin, S.A. Jones, D. Hawkins-Brown, K.I. MacKenzie, A. LaTour, Y. Liu, C.D. Klaassen, K.K. Brown, J. Reinhard, T.M. Willson, B.H. Koller, S.A. Kliewer, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 3369–3374.
[102] G.L. Guo, J. Staudinger, K. Ogura, C.D. Klaassen, Mol. Endocrinol. 61 (2002) 832–839.
[103] W. Xie, A. Radominska-Pandya, Y. Shi, C.M. Simon, M.C. Nelson, E.S. Ong, D.J. Waxman, R.M. Evans, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 3375–3380.
[104] D. Jung, B. Hagenbuch, L. Gresh, M. Pontoglio, P.J. Meier, G.A. Kullak-Ublick, J. Biol. Chem. 276 (2001) 37206–37214.
[105] D. Jung, M. Podvinec, U.A. Meyer, D.J. Mangelsdorf, M. Fried, P.J. Meier, G.A. Kullak-Ublick, Gastroenterology 122 (2002) 1954–1966.

[106] J.S. Glavy, S.M. Wu, P.J. Wang, G.A. Orr, A.W. Wolkoff, J. Biol. Chem. 275 (2000) 1479–1484.
[107] G.L. Guo, C.D. Klaassen, J. Pharmacol. Exp. Ther. 299 (2001) 551–557.
[108] D.Q. Shih, M. Bussen, E. Sehayek, M. Ananthanarayanan, B.L. Shneider, F.J. Suchy, S. Shefer, J.S. Bollileni, F.J. Gonzalez, J.L. Breslow, M. Stoffel, Nat. Genet. 27 (2001) 375–382.
[109] G.P. Hayhurst, Y.H. Lee, G. Lambert, J.M. Ward, F.J. Gonzalez, Mol. Cell. Biol. 21 (2001) 1393–1403.
[110] C.J. Sinal, M. Tohkin, M. Miyata, J.M. Ward, G. Lambert, F.J. Gonzalez, Cell 102 (2000) 731–744.
[111] L.A. Denson, E. Sturm, W. Echevarria, T.L. Zimmerman, M. Makishima, D.J. Mangelsdorf, S.J. Karpen, Gastroenterology 121 (2001) 140–147.
[112] R.G. Tirona, B.F. Leake, G. Merino, R.B. Kim, J. Biol. Chem. 276 (2001) 35669–35675.
[113] T. Nozawa, M. Nakajima, I. Tamai, K. Noda, J. Nezu, Y. Sai, A. Tsuji, T. Yokoi, J. Pharmacol. Exp. Ther. 302 (2002) 804–813.
[114] J. Lee, J.L. Boyer, Semin. Liver Dis. 20 (2000) 373–384.
[115] P. Fickert, G. Zollner, A. Fuchsbichler, C. Stumptner, C. Pojer, R. Zenz, F. Lammert, B. Stieger, P.J. Meier, K. Zatloukal, H. Denk, M. Trauner, Gastroenterology 121 (2001) 170–183.
[116] T. Gerloff, A. Geier, B. Stieger, B. Hagenbuch, P.J. Meier, S. Matern, C. Gartung, Gastroenterology 117 (1999) 1408–1415.
[117] A. Geier, C.G. Dietrich, F. Lammert, T. Orth, W.J. Mayet, S. Matern, C. Gartung, J. Hepatol. 36 (2002) 718–724.
[118] M. Oswald, G.A. Kullak-Ublick, G. Paumgartner, U. Beuers, Liver 21 (2001) 247–253.
[119] G. Lee, S. Dallas, M. Hong, R. Bendayan, Pharmacol. Rev. 53 (2001) 569–596.
[120] H.M. Wain, E.A. Bruford, R.C. Lovering, M.J. Lush, M.W. Wright, S. Povey, Genomics 79 (2002) 464–470.